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Left Ventricular Diastolic Function in Hypertension: Relation to Left Ventricular Mass and Systolic Function

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Initial studies of diastolic cardiac function in hypertension demonstrated that slowing of the maximal rate of left ventricular filling occurred before alterations in either ejection fraction or cardiac output. The present study was undertaken to determine: 1) the relation between hypertension, increased left ventricular mass and impaired left ventricular filling, and 2) the correlation between abnormalities in left ventricular diastolic function and its systolic performance. Eleven normal subjects (Group 1), 5 hypertensive patients without evidence of left ventricular hypertrophy (Group 2) and 18 hypertensive patients with increased left ventricular mass by echocardiography (Group 3) were studied by M-mode echocardiography, radionuclide (technetium-99m human serum albumin) first pass technique and gated blood pool scintigraphy.

Indexes of systolic function (ejection fraction, maximal rate of ejection and percent left ventricular shortening) were essentially similar in hypertensive and normotensive subjects. No correlation was found between systolic blood pressure and left ventricular mass ($r = 0.20$, not significant). Maximal rate of left ventricular filling (P dV/dt) and fast filling fraction decreased progressively from Group 1 to Group 3 (2.36 ± 0.4 [mean $\pm$ standard deviation], 2.17 ± 0.3 and 1.97 ± 0.4 s^{-1}, respectively, for P dV/dt and 46 ± 7, 48 ± 9 and $38 \pm 11\%$, respectively, for fast filling fraction); the difference from values in normal subjects reached statistical significance in hypertensive patients with left ventricular hypertrophy. Left ventricular maximal filling rate correlated inversely with left ventricular mass and left ventricular end-systolic diameter ($r = -0.74$), but positively with left ventricular fractional shortening and ejection fraction ($r = 0.70$).

These results suggest that impairment of early left ventricular filling develops in relation to left ventricular hypertrophy in hypertension and that it can be detected even before definite evidence of systolic cardiac impairment is present.

Recent noninvasive techniques have allowed evaluation of the diastolic function of the heart in asymptomatic patients (1–3). A slow left ventricular filling rate was found in coronary artery disease (1,3) and in hypertension (2), before alterations in systolic function. Inasmuch as a slow rate of left ventricular filling is related to left ventricular relaxation, these initial investigations could help explain the occurrence of isolated left atrial abnormality in hypertension (4,5). However, these early studies of left ventricular filling in hypertension did not report on the simultaneous structural changes in the left ventricle, particularly the presence or absence of left ventricular hypertrophy.

The present study was undertaken to determine the relation, if any, between the elevation in arterial pressure with and without increase in left ventricular mass and the alteration of left ventricular filling. In particular, it was important to determine whether abnormalities in diastolic function of the heart were dependent on structural factors, such as left ventricular hypertrophy, and whether there was any correlation between altered left ventricular filling and variations in systolic function. This involved a combined approach including study of cardiac function by radionuclide techniques and determination of cardiac mass and left ventricular wall stress by echocardiography. Thus, both the functional and structural aspects of alterations in left ventricular filling could be examined noninvasively in patients with hypertension.

Methods

Study Group

Thirty-four consecutive subjects were studied: 11 normotensive volunteers and 23 patients with untreated hypertension who did not show any history or evidence of coro-

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nary artery disease, diabetes mellitus, renal insufficiency or heart failure. More specifically, no patient had electrocardiographic signs of prior myocardial infarction or showed abnormality of wall motion on radionuclide examination. In all but four patients, renal function was within normal for the laboratory; in these four patients, serum creatine level varied between 1.7 and 2.1 mg/100 ml. The purpose of the study, the noninvasive nature of the tests and the minimal radioactivity exposure were explained in detail to all patients, and they gave free, informed consent to the study. The protocol for investigation of cardiac performance in hypertension was approved by the Institutional Review Board. The subjects were classified into three groups, according to blood pressure status and echocardiographic data.

Group 1. This group comprised 11 normotensive subjects without evidence of heart disease or left ventricular hypertrophy. There were six women and five men with a mean age of 37 years (range 21 to 62).

Group 2. This group comprised five patients with well documented established hypertension and no clinical, electrocardiographic or echocardiographic evidence of left ventricular hypertrophy. There were three women and two men with a mean age of 48 years (range 34 to 68).

Group 3. This group comprised 18 patients with established essential hypertension. There were nine women and nine men with a mean age of 49 years (range 33 to 72). All patients in this group had echocardiographic evidence (M-mode) of left ventricular hypertrophy based on classic criteria (6). All were either untreated or discontinued medications for at least 2 weeks before the study. Six had concentric left ventricular hypertrophy and 12 had asymmetric (isolated) septal hypertrophy.

Study Protocol

The protocol consisted of two sequential studies performed on the same day or within a 24 hour interval. The first was the determination of cardiac output, ejection fraction and other hemodynamic indexes by radionuclide technique. The second was M-mode echocardiography performed with two-dimensional echocardiographic monitoring for calculation of left ventricular mass, left ventricular stress and fractional shortening.

Radionuclide hemodynamic study. All studies were performed in the morning after an overnight fast (except for water). After 30 minutes of supine rest, plasma volume was determined by 125-iodine–labeled human serum albumin using 10 minutes of equilibration, as previously described in detail (7). Total blood volume was derived from plasma volume and simultaneously determined hematocrit (7).

Hemodynamic studies were then performed in duplicate using the radioisotope (technetium-99m human serum albumin) first pass technique. Details of the radioisotope technique and its validation in our laboratory by comparison with the dye-dilution and thermodilution methods have been previously described (8–10). Cuff arterial pressure was determined in the arm by auscultation, the diastolic pressure was recorded as Korotkoff phase V (11). Previous studies from this center and others (12,13) have shown that auscultated systolic brachial pressure correlated very closely ($r = 0.90$, probability [p] < 0.001 in our experience) with directly obtained intraventricular systolic pressure in patients without aortic stenosis. Heart rate was obtained from continuous recordings of a lead II electrocardiogram. At least 10 to 12 blood pressure and heart rate recordings were obtained during the study; average values were used for derivation of hemodynamic indexes.

Derived hemodynamic indexes were calculated by standard formulas; they included mean arterial pressure, cardiac index, stroke index and total peripheral resistance (8,9). The measurement of pulmonary mean transit time allowed derivation of cardiopulmonary volume (10).

Left ventricular volume curves and ejection fraction were obtained by imaging (gated blood pool technique) during the equilibrium phase after the first pass study, thus making use of the same circulating radioisotope. The left ventricular volume curve was analyzed (PDP-15 system) to measure ejection fraction and maximal rates of left ventricular ejection (negative = N dV/dt) and left ventricular filling (positive = P dV/dt) as described previously in detail (2). In summary, left ventricular ejection fraction was calculated by subtracting the left ventricular end-systolic counts from left ventricular end-diastolic counts, and dividing the result by left ventricular end-diastolic counts. For calculation of the rates of ejection and filling, Fourier analysis was applied to fit curve to the data points (16 in our system) by the method of least squares. The time derivative of the curve was computed by using the Fourier transform technique as a global estimate of the tangent to the curve at each data point. Because this curve represents the radioactivity counts as a mathematical function of time, the derivatives were expressed in counts per second. The negative derivatives corresponded to the decrease in counts of ejection phase and the positive derivatives corresponded to the increase in counts of filling phase.

In this analysis, we examined the largest negative and positive derivatives. These derivatives were scaled by maximal absolute counts equivalent to the end-diastolic counts to compensate for variation in injected dose and efficiency of the acquisition system. The units of these new variables were, therefore, expressed in units of fractional change per second or hertz (Hz). These variables are proportional to the change in volume/unit time and hence referred to as dV/dt. The filling phase was further analyzed to measure the fraction of fast filling and the fraction of slow filling by a modification of the index described by Reduto et al. (3).

Echocardiographic techniques. The technique for echocardiographic recordings and measurement of relevant indexes has also been previously described (6). In all hy-

pertensive patients, M-mode echocardiography was performed while monitoring the ultrasonic beam direction by two-dimensional view on a TV screen using Toshiba apparatus (Toshiba model SSH-10A) and a 2.4 MHz transducer. The examinations were done in a slightly tilted position to obtain both the septum and posterior wall in the same view at the tip of the mitral valve.

Measurements of left ventricular diameters were made at end-diastole, marked by the beginning of the QRS complex, and at end-systole, as determined from the shortest left ventricular internal diameter. Measurements were obtained from an average of at least six consecutive cardiac cycles using a programmable calculator (Numonics model 1239). The calculation of left ventricular meridional wall stress was based on principles derived by Grossman et al. (14) and verified by Wilson et al. (13), using the echocardiographic determination of left ventricular diameters and wall thickness and auscultating brachial systolic pressures. Peak systolic wall stress was calculated from the systolic blood pressure, end-diastolic left ventricular diameter and corresponding posterior wall thickness. End-systolic wall stress was calculated from systolic blood pressure, end-systolic left ventricular diameter and corresponding posterior wall thickness. Normal values in our laboratory averaged (mean ± standard deviation) 60 ± 14 × 10^3 dynes/cm^2 per s for end-systolic wall stress, and 169 ± 27 × 10^3 dynes/cm^2 per s for peak systolic wall stress.

The diagnosis of left ventricular hypertrophy from M-mode echocardiography was based principally on a left ventricular mass index of 95 g/m^2 or greater (>2 standard deviations from the normal mean in our laboratory) (6,15). The diagnosis was further substantiated by left ventricular posterior end-diastolic wall thickness or end-diastolic septal wall thickness, or both, of 1.2 cm or greater.

Analysis of data. The subdivision of subjects into groups was used in the first analysis to examine the significance of differences between normotensive and hypertensive subjects and between patients with and without left ventricular hypertrophy. However, because patients with hypertension form a continuum in relation to extent of cardiac involvement, analyses were performed to examine the correlates of left ventricular filling rate in all patients as a group.

Calculations of averages, paired and unpaired *t* tests and correlation coefficients were performed by standard methods (16). Values reported are means ± standard deviation. Differences were considered statistically significant when probability (p) was less than 0.05. Data were analyzed with the help of PROPHET, a national computer service resource supported by the National Institutes of Health.

Results

Hemodynamic Data (Table 1)

Both hypertensive groups had, by definition, higher systolic and diastolic arterial pressure than the normal volunteers, but there was no significant difference in pressure between the two hypertensive groups. No significant difference was found among all groups in cardiac index, mean transit time or cardiopulmonary volume. The increase in arterial pressure in hypertensive subjects was therefore related to an increase in total peripheral resistance (30 μm^2 in Group 1 (normal subjects), 52 μm^2 in Group 2 (hypertension without left ventricular hypertrophy) and 49 μm^2 in Group 3 (hypertension with left ventricular hypertrophy; $p < 0.01$, between Group 1 and either Group 2 or 3). Heart rate was higher in the hypertensive patients than in the normotensive volunteers (Table 2). Stroke index was significantly lower in the hypertensive patients compared with normal subjects, as has been frequently noted previously (17).

Indexes of systolic function (aside from stroke volume) showed no significant difference between normotensive and hypertensive groups. Thus, ejection fraction, mean rate of left ventricular ejection and left ventricular percent shortening were essentially similar in hypertensive patients and normotensive subjects (Tables 1 and 2). The lower stroke index was therefore related either to the more rapid heart rate or to the increased pressure in hypertensive patients rather than to myocardial dysfunction (17).

Left Ventricular Diastolic Function

Indexes of left ventricular filling rate. The most marked difference between the normotensive and hypertensive patients was noted in the various indexes of left ventricular filling (Table 2). Maximal rate of left ventricular filling (P dV/dt) decreased progressively: values in the normotensive subjects (Group 1) were higher than in hypertensive patients without left ventricular hypertrophy (Group 2) (2.36 ± 0.37 versus 2.17 ± 0.27 Hz) and reached a minimum of 1.97 ± 0.44 Hz in Group 3 patients (hypertensive patients with left ventricular hypertrophy). The reduction in P dV/dt from normal reached statistical significance only in Group 3 ($p < 0.05$); however, patients in Group 2 had values intermediate between those of normal subjects and hypertensive patients with left ventricular hypertrophy, so that their group average was not significantly different from that of the other two groups. Correction for heart rate did not alter these results. In fact, the reduction in dV/dt in Group 2 attained borderline statistical significance from normal (Table 3). Fast filling fraction also progressively declined from Group 1 to Group 3. In contrast, the slow filling fraction increased progressively among the three groups: 11% in Group 1, 15% in Group 2 and 21% in Group 3 (Table 2).

Correlates of altered left ventricular filling in hypertensive patients. A highly significant negative correlation was found between P dV/dt and end-systolic left ventricular wall stress (Fig. 1). This dependence of left ventricular filling on end-systolic wall stress was further studied in relation to each of the values entering in the calculation of

Table 1. Systemic Hemodynamics

Group	SBP	DBP	CI	SI	TPR	MTT	CPV
Group 1: (normal subjects; n = 11)	114 ± 25	73 ± 7	2,914 ± 458	45 ± 4.8	30 ± 4	8.6 ± 1.5	732 ± 129
Group 2: (hypertensive subjects without LVH; n = 5)	174* ± 31	107* ± 8	2,522* ± 195	34* ± 1.4	52* ± 8	9.2* ± 4	655 ± 264
Group 3: (hypertensive subjects with LVH; n = 18)	156* ± 25	103* ± 14	2,592* ± 634	36* ± 7.6	49* ± 10	8.5* ± 2	683 ± 225

*Probability (p) < 0.01 versus normal subjects; differences between the two hypertensive groups were not significant. CI = cardiac index (liters/min per m^2); CPV = cardiopulmonary volume (ml); DBP = diastolic blood pressure (mm Hg); LVH = left ventricular hypertrophy; MTT = pulmonary mean transit time (seconds); SBP = systolic blood pressure (mm Hg); SI = stroke index (ml/m^2); TPR = total peripheral resistance (U·m^2).

stress, namely systolic pressure, end-systolic volume or left ventricular diameter and left ventricular wall thickness in end-systole. No correlation was found between peak positive dV/dt and systolic blood pressure (Fig. 2). End-systolic left ventricular diameter correlated significantly with positive dV/dt ($r = -0.74$) (Fig. 3). We have chosen to base our correlation on left ventricular diameter at end-systole diameter (LVESD) rather than left ventricular end-systolic volume (ESV) because: 1) it is this diameter that enters in the calculation of left ventricular end-systolic wall stress, and 2) it is a directly determined value rather than a calculated number ($ESV = [LVESD]^3$). However, the same correlation ($r = -0.71$, $p \leq 0.001$) was obtained when left ventricular end-systolic volume was used. Finally, left ventricular mass correlated inversely with peak dV/dt (Fig. 4), meaning that the maximal rate of left ventricular filling was slower when the left ventricular mass was higher; correlations with left ventricular wall thickness ($r = -0.39$ at best when septal wall in end-diastole was used) did not reach statistical significance. Similarly, no significant correlation was found between peak positive dV/dt and either diastolic blood pressure ($r = -0.21$) or peak systolic stress ($r = -0.22$).

Relation of Diastolic Filling to Systolic Performance

Left ventricular systolic performance was evaluated from two indexes, the standard left ventricular fractional shortening (%Sh) and a more recently introduced index of "contractility" end-systolic pressure/end-systolic volume (ESP/ESV). In this study we utilized the ratio of systolic blood pressure to left ventricular end-systolic diameter to avoid the inaccuracies associated with calculations of end-systolic volume from end-systolic diameter obtained from the short axis only. We and others (12,13) have previously found a significant correlation between brachial cuff systolic pressure and left ventricular systolic pressure.

Both indexes of systolic performance correlated significantly ($p < 0.001$), with the maximal rate of left ventricular filling: $r = 0.70$ for the correlation between peak positive

Table 2. Cardiac Function Indexes

	Ejection Indexes		LV Filling Indexes			
Group	EF	N dV/dt	FF	SF	P dV/dt	HR
Group 1: (normal subjects; n = 11)	51 ± 8	2.20 ± 0.25	46 ± 7	11 ± 4	2.36 ± 0.37	59 ± 8
Group 2: (hypertensive subjects without LVH; n = 5)	54 ± 10	2.68 ± 0.56	48 ± 9	15 ± 7	2.17 ± 0.27	66 ± 8
Group 3: (hypertensive subjects with LVH; n = 18)	48 ± 9	2.27 ± 0.42	38† ± 11	21* ± 9	1.97† ± 0.44	68* ± 8

*$p < 0.01$, †$p < 0.05$ versus normal subjects; differences between the two hypertensive groups were not significant. EF = ejection fraction (%); FF = fast filling fraction (%); HR = heart rate (beats/min); LV = left ventricular; LVH = left ventricular hypertrophy; N dV/dt and P dV/dt = maximal rate of left ventricular ejection (negative) and maximal rate of left ventricular filling (positive), respectively (Hz); SF = slow filling fraction (%).

Table 3. Effect of Correction for Heart Rate on Maximal Left Ventricular Diastolic Filling

Group	P dV/dt (Hz)		
	Uncorrected	Normalized for Heart Rate	Normalized for RR Interval
Group 1: (normal subjects)	2.36 ± 0.37	2.42 ± 0.48	2.39 ± 0.41
Group 2: (hypertensive subjects without LVH)	2.17 ± 0.27	1.96 ± 0.11	2.06 ± 0.17
Group 3: (hypertensive subjects with LVH)	1.97 ± 0.44	1.75 ± 0.48	1.85 ± 0.45
p Value			
1 vs. 2	NS	<0.05	0.08 (NS)
1 vs. 3	<0.05	<0.01	<0.01
2 vs. 3	NS	NS	NS

LVH = left ventricular hypertrophy; NS = not significant; P dV/dt = maximal left ventricular diastolic filling rate.

dV/dt and fractional shortening of the left ventricle (Fig. 5), and r = 0.69 for the correlation between peak positive dV/dt and the left ventricular contractility index (ratio of systolic blood pressure to left ventricular systolic end diameter) (Fig. 6).

Discussion

The present study has confirmed in a larger number of patients the first reports (2) of early impairment of left ventricular filling in hypertension, an impairment often found before any evidence of reduced cardiac output or ejection fraction. In addition, the concomitant determination of ventricular volume curves and of echocardiographic left ventricular indexes has allowed an examination of the correlates of that impairment. The reduction in peak rate of early left ventricular filling was related to left ventricular mass and left ventricular end-systolic diameter, not to arterial pressure levels themselves. Although the degree of systolic performance and the rate of early left ventricular filling correlated significantly with each other, ejection fraction and left ventricular fractional shortening remained within normal limits in most patients, whereas the rate of left ventricular filling was significantly reduced. Thus, we could again determine that cardiac abnormalities in patients with hypertension had their first measurable expression in abnormalities of left ventricular filling rather than in systolic performance. These findings further underline the early cardiac involvement in hypertension recently described in experimental models (18) and hypertensive adolescents (19).

Figure 1. Correlation between peak rate of left ventricular filling (PDV/DT) and left ventricular end-systolic stress (ESS) in patients with hypertension. **Closed circles** indicate 5 hypertensive patients without evidence of left ventricular hypertrophy (Group 2) and **open circles** indicate 18 hypertensive patients with such evidence (Group 3). p = probability; r = correlation coefficient.

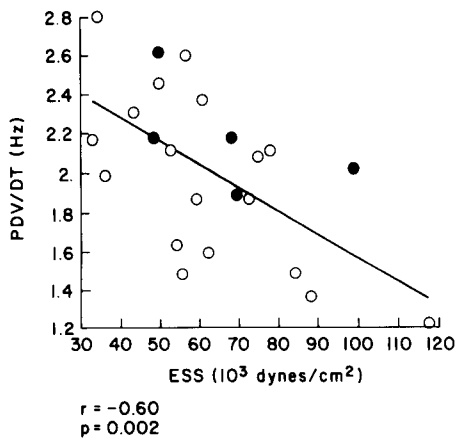
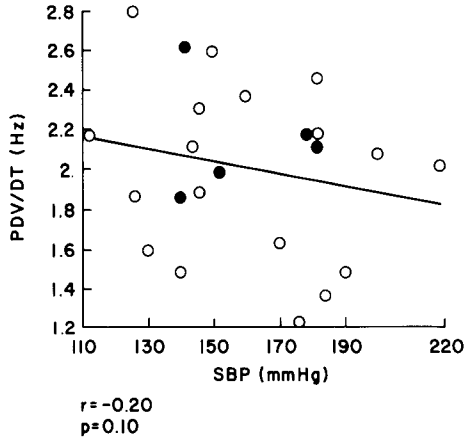


Figure 2. Lack of correlation in hypertensive patients between peak rate of left ventricular filling (PDV/DT) and systolic blood pressure (SBP). Symbols and abbreviations as in Figure 1.



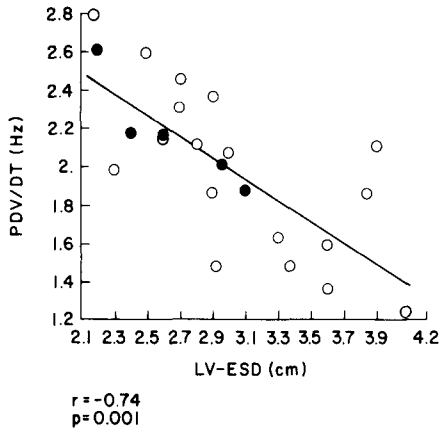


Figure 3. Inverse correlation of echocardiographically determined left ventricular end-systolic diameter (LV-ESD) and peak rate of left ventricular filling (PDV/DT) determined by radionuclide technique in hypertensive patients. Symbols and abbreviations as in Figure 1.

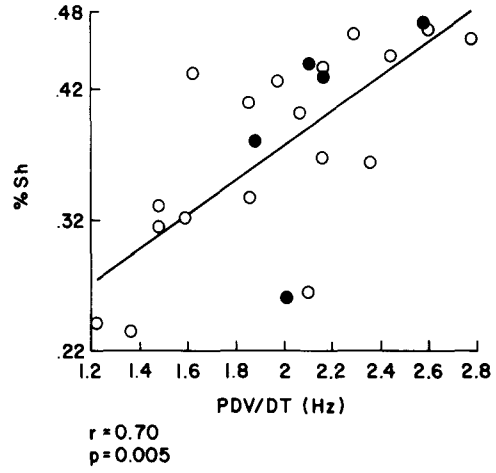
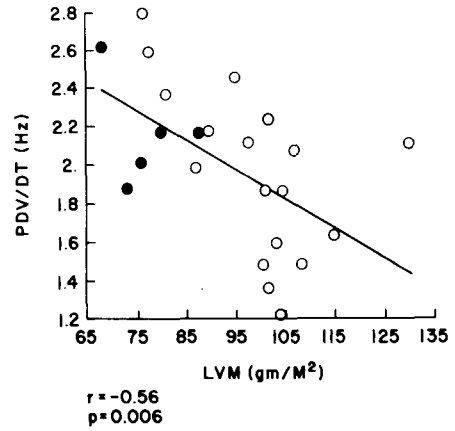


Figure 5. Correlation between an index of left ventricular diastolic function (PDV/DT) and an index of left ventricular systolic performance (%Sh = left ventricular percent shortening) in hypertensive patients. Symbols and abbreviations as in Figure 1.

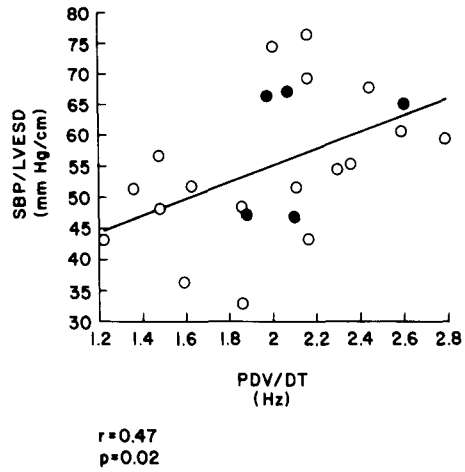
Functional correlates of left ventricular filling rate. The reduction in early left ventricular filling was correlated significantly with left ventricular mass (Fig. 4) and to a lesser degree with left ventricular wall thickness. This implies that it was influenced not only by structural changes (wall thickness), but also by the functional condition of the left ventricle. In that regard, the influence of left ventricular end-systolic diameter was found to be significantly higher than that of systolic blood pressure levels. However, the role of systolic blood pressure might have been underrated by the fact that only peak systolic pressure was recorded by auscultation and not left ventricular end-systolic pressure. Whatever the case, our findings confirm the conclusions of Brutsaert (20) regarding the importance of end-systolic events in determining the rate of left ventricular relaxation in human beings.

Figure 4. Inverse correlation between left ventricular mass (LVM) in g/m^2 and peak rate of left ventricular filling (PDV/DT) in hypertensive patients. Symbols and abbreviations as in Figure 1.



Relation to systolic function. The importance of diastolic relaxation and filling to adequate systolic function has not always been sufficiently appreciated. Systolic performance depends to a large degree on adequate filling, which is related to the rapidity, extent and homogeneity of relaxation during the preceding diastole. To these relations, which may be considered as "mechanical" or "pump priming" factors, one can add more subtle influences of various factors on myocardial contractility (21). Although the impact of adrenergic factors on ventricular contraction is well known, their influence on ventricular relaxation is less well recognized. Sonnenblick et al. (22) showed the marked influence of sympathetic tone on relaxation of papillary muscles. Fouad et al. (23) showed the practical importance of these adre-

Figure 6. Correlation between an index of left ventricular contractility (systolic blood pressure/left ventricular end-systolic diameter [SBP/LVESD]) and peak rate of left ventricular filling (PDV/DT).



nergic effects during treatment of hypertension by beta-adrenergic blockade. In this study, the close correlation found between indexes of overall systolic function or left ventricular contractility (systolic blood pressure/end-systolic diameter) and left ventricular filling rate (Fig. 5 and 6) implies that left ventricular relaxation and systole can be influenced by the same neurohumoral factors. Hence, an increased sympathetic tone that improves left ventricular contraction will also enhance relaxation rate and filling. Clinically, the abnormality associated with hypertension appears first in measures of early or maximal rate of left ventricular filling. Clearly, more studies are needed to determine if measures designed to improve left ventricular filling will also lead to better left ventricular performance.

In summary, slowing of maximal left ventricular filling rate was found to be common in hypertensive patients, even before signs of decreased systolic performance. The reduction in maximal filling rate was related to both left ventricular structural changes associated with hypertension and to the alterations in ventricular systolic performance. In particular, the conditions determining left ventricular end-systolic stress played a significant role in determining the rate of early left ventricular filling.

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